# Proposed Decision Memo for Extracorporeal Photopheresis (CAG-00324R)

# **Decision Summary**

The Centers for Medicare and Medicaid Services (C	CMS) proposes that extracorpor	real photopheresis is reasonable
and necessary for:		

- 1. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and
- 2. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

CMS proposes that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

All other indications remain non-covered.

Back to Top

# **Proposed Decision Memo**

TO: Administrative File: CAG- 00324R Extracorporeal Photopheresis

Printed on 4/13/2012. Page 1 of 52

FROM:

Steve Phurrough, MD, MPA Director, Coverage and Analysis Group

Marcel Salive, MD, MPH Director, Division of Medical and Surgical Services

Susan Harrison, MPP Lead Analyst, Division of Medical and Surgical Services

Lori Paserchia, MD Lead Medical Officer, Division of Medical and Surgical Services

Ross Brechner, MD, MS, MPH Medical Officer, Division of Medical and Surgical Services

Sandy Jones, RN Analyst, Division of Medical and Surgical Services

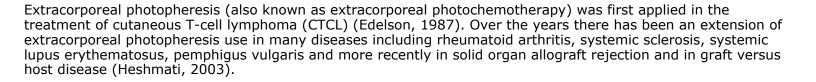
Beverly Lofton, MHA Analyst, Division of Medical and Surgical Services

SUBJECT: Proposed Decision Memorandum for Extracorporeal

Photopheresis

DATE: October 4, 2006

I. Proposed Decision
The Centers for Medicare and Medicaid Services (CMS) proposes that extracorporeal photopheresis is reasonable and necessary for:
1. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and
2. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.
CMS proposes that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.
All other indications remain non-covered.
II. Background
A. Background of the Procedure



Extracorporeal photopheresis is a medical procedure in which a patient's white blood cells are exposed first to a drug called 8-methoxypsoralen (8-MOP) and then to ultraviolet A (UVA) light. The procedure starts with the removal of the patient's blood, which is centrifuged to isolate the white blood cells. The drug is typically administered directly to the white blood cells after they have been removed from the patient (referred to as ex vivo administration) but the drug can alternatively be administered directly to the patient before the white blood cells are withdrawn. After UVA light exposure, the treated white blood cells are then re-infused into the patient.

Extracorporeal photopheresis is usually performed on two consecutive days at four-week intervals with clinical evaluation at six months to determine response. The duration of treatment varies significantly depending on the medical condition being treated, and the patient's response to the treatments.

Today extracorporeal photopheresis is commonly administered via the UVAR® XTS<sup>™</sup> system, which is an FDA-approved wholly-contained, automated processing system manufactured by Therakos, Inc. This system is a single unit that handles the collection of the patient's blood, the isolation of the white blood cells, and the ex vivo administration of 8-MOP and UVA. The UVAR® XTS<sup>™</sup> system evolved from the FDA-approved UVAR® system, which used the oral formulation of 8-MOP. Other systems and protocols have been used to administer extracorporeal photopheresis, however. In this decision memorandum, CMS is evaluating the extracorporeal photopheresis procedure, and not a specific system for administering extracorporeal photopheresis.

The exact mechanism of action of extracorporeal photopheresis is still elusive (Edelson, 1987). The role of UVA is to activate the normally inert 8-MOP. The activated 8-MOP molecules bind with the DNA of the white blood cells, which kills the cells. The dead white blood cells, once reinfused into the patient, stimulate the multiple different cells and proteins of the patient's immune system in a series of cascading reactions. This activation of the immune system then impacts the medical condition being treated; however, the precise manner in which the medical condition is affected is still largely unknown but is believed to vary by condition (Therakos, Inc. 2006). Hence, extracorporeal photopheresis is a procedure that attempts to negatively impact the ability of specific immune cells to function but without inducing a general state of immunosuppression (Dall'Amico, 1995).

#### **B. Disease Summary**

# 1. Refractory Acute Cardiac Allograft Rejection

Printed on 4/13/2012. Page 4 of 52

Cardiac transplantation is a procedure that involves the replacement of a failing heart with another heart from a suitable donor. One potential complication of cardiac transplantation is rejection of the transplanted heart. During rejection, the cardiac transplant recipient's immunological system produces cells and proteins that rightly recognize the transplanted heart as "foreign" and therefore attack it. Due to the serious nature of rejection, the patient is routinely started on immunosuppressive drug therapy immediately after the transplantation in an attempt to prevent the onset of rejection.

Although acute rejection of the transplanted heart can occur within days, months or years of transplantation (www.heart-transplant.org 2006), rejection most frequently occurs during the first month after transplantation (Patel, 2004). Histological rejection refers to the microscopic detection of the immunological attack on the heart during an episode of rejection. This type of rejection is associated primarily with specific immunologic cells called T lymphocytes and is referred to as cell-mediated rejection. A patient may or may not have symptoms in the presence of histological rejection. In fact, most patients with histological changes consistent with rejection have no change in heart function that could lead to symptoms (Hosenpud, 2005).

The chance that a patient may not have symptoms due to acute rejection mandates that routine testing be performed to detect the presence of rejection and to measure the effect of immunosuppressive drug treatment (Patel, 2004). An endomyocardial biopsy (EMB) is the gold standard for monitoring for the presence or absence as well as the severity of histological rejection. The degree of rejection present in the heart muscle has traditionally been graded as noted in the following table from the International Society of Heart and Lung Transplantation (ISHLT) (Billingham, 1990).

#### **Billingham Classification for Grading Endomyocardial Biopsy**

Grade	Degree of Rejection
0	None
1	A: focal (perivascular or interstitial) infiltrate without necrosis B: diffuse but sparse infiltrate without necrosis
2	One focus only with aggressive infiltration and/or focal myocyte damage
3	A: multifocal aggressive infiltrates and/or myocyte damage B: diffuse inflammatory process with necrosis

Grade	Degree of Rejection
4	Diffuse aggressive polymorphous +/- infiltrate +/- edema +/- hemorrhage +/- vasculitis, with necrosis

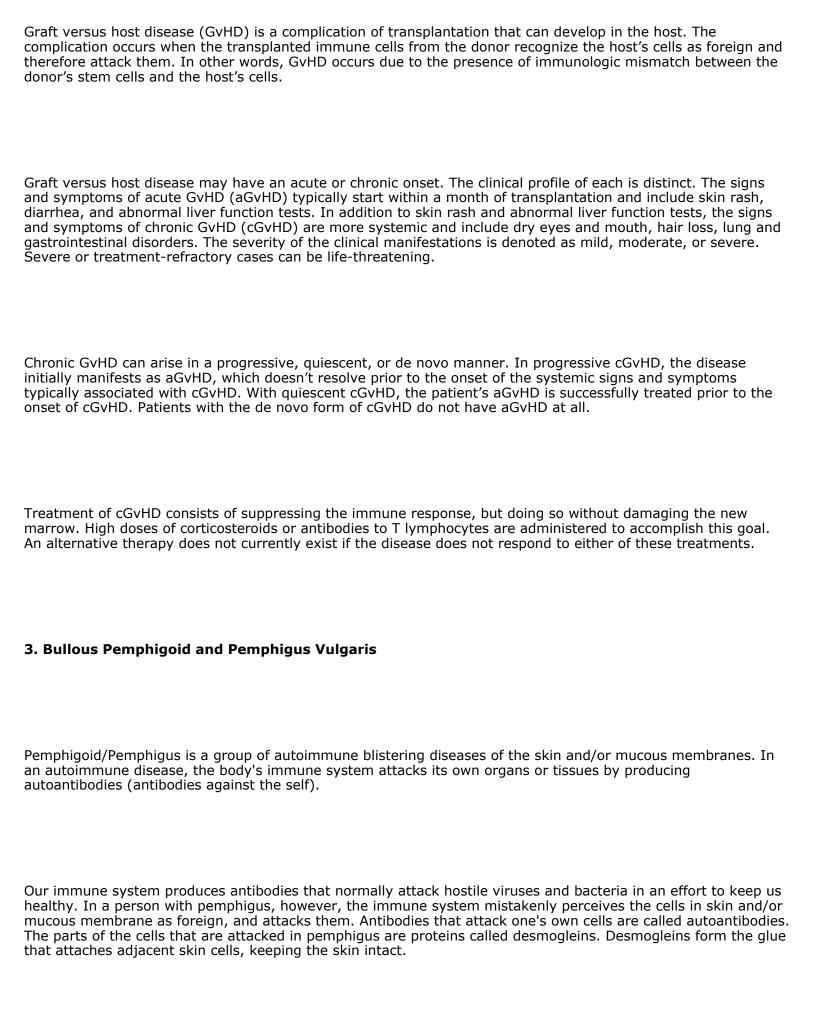
Once diagnosed, the management of acute rejection is dependent on the severity of the signs, symptoms, and changes in the histology (Patel, 2004). The majority of episodes of histological rejection are effectively treated with modification of the immunosuppressive drug therapy (Hosenpud, 2005). Grade 1A/B or 2 rejection without clinical signs or symptoms generally does not lead to a change in immunosuppression management. Steroids are typically administered for an asymptomatic Grade 3A/B rejection. Asymptomatic Grade 4 or symptomatic Grade 3A/B rejection is treated with anti-rejection drugs such as OKT3, daclizumab, basaliximab or high doses of methylprednisolone. For a patient who has persistent cell-mediated rejection that is unresponsive (i.e., refractory) to all attempts at treatment with the typical types and doses of drugs, extracorporeal photopheresis has been proposed and used as therapy (Patel, 2004).

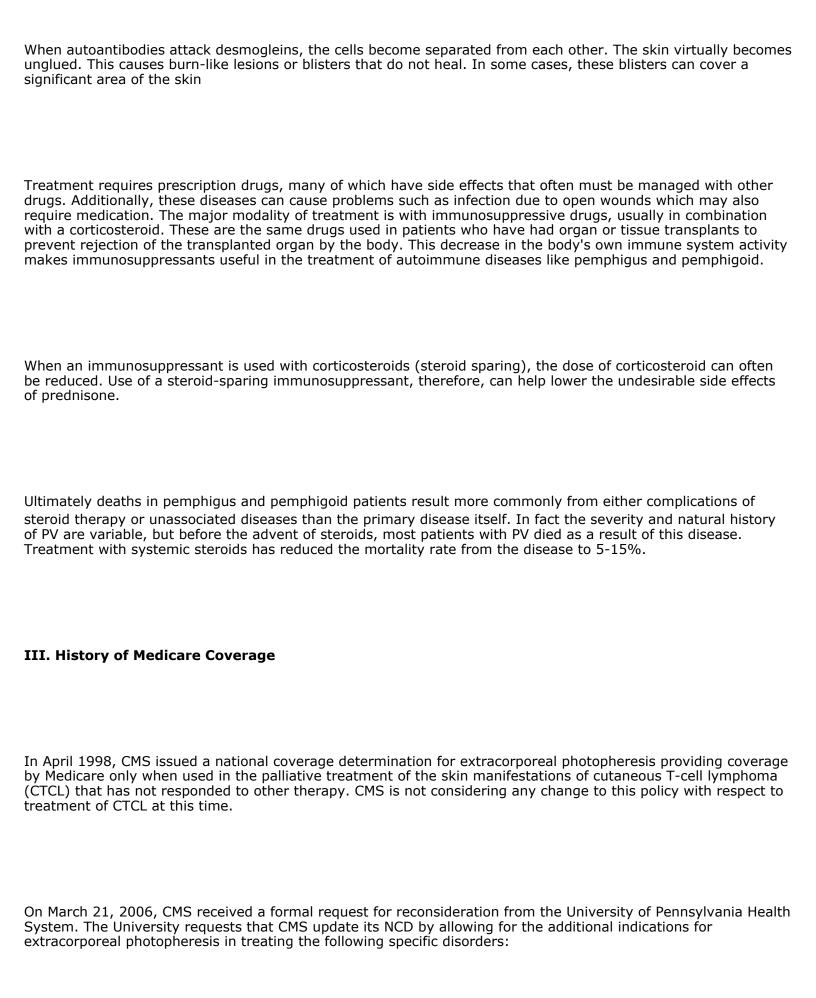
Cardiac transplant rejection can result in significant morbidity and mortality. The increased doses of immunosuppressive drugs required to treat an episode of severe rejection substantially increase the risk of severe infections and malignancies (Dall'Amico, 1997). Recurrent episodes of rejection impact the patient's quality of life as well as graft survival (Guinti, 1999), which can ultimately lead to death if the patient is not retransplanted (Costanzo-Nordin, 1992).

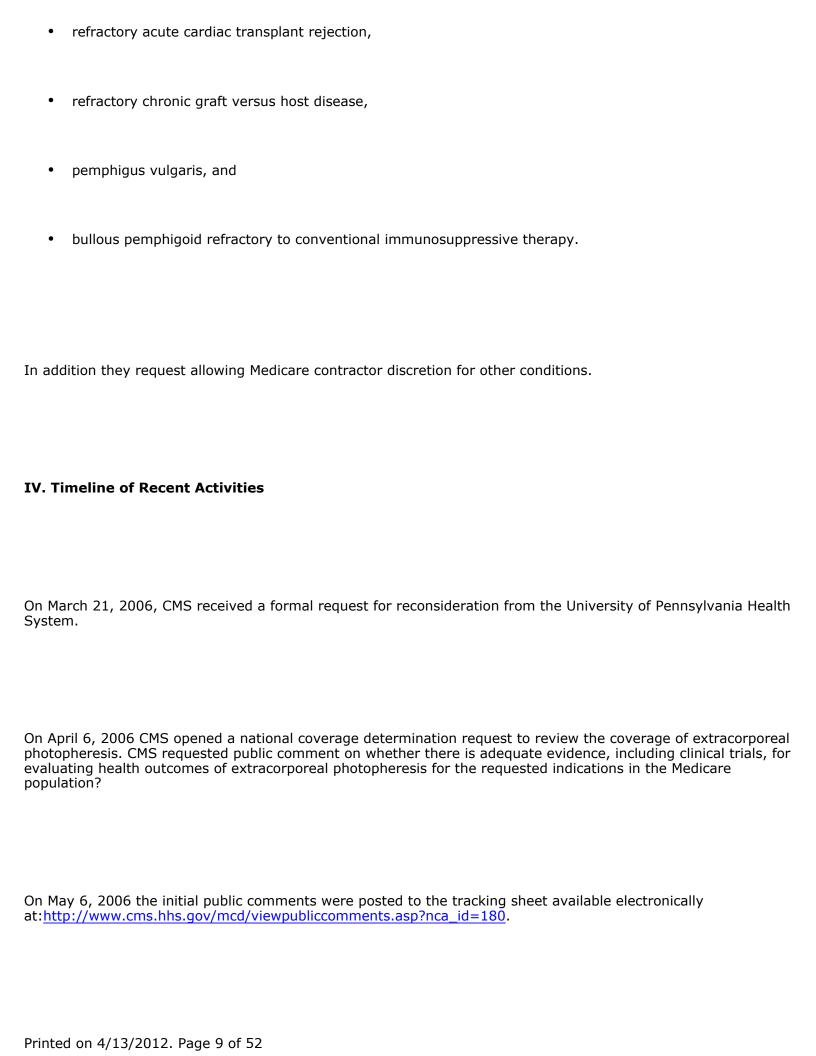
## 2. Refractory Chronic Graft versus Host Disease (cGvHD)

Allogeneic hematopoietic cell transplantation (aHCT) is performed to treat and potentially cure a variety of malignant or non-malignant diseases. In an aHCT, cells are taken from the bone marrow or blood of a human donor and administered to a human host. Prior to transplantation, the host's bone marrow is destroyed with chemotherapy or radiation in order to eradicate the cancer cells and to prepare the host to accept the transplanted cells. After transplantation, immunosuppressive drugs are administered to the host to permit the new cells to implant without being destroyed by the host's immune system.

Unless the donor and host are identical twins, the genetic profile of the donor and of the host is similar but not identical. The degree of similarity between the two genetic profiles is an important factor in determining the risk of triggering immunologically-mediated complications after the transplantation. For any transplantation, it is critical to match the donor's genetic profile as much as possible to the host's genetic profile in order to minimize this risk.







#### V. FDA Status

In 1999, The FDA approved UVADEX® (methoxsalen) Sterile Solution, which is indicated for extracorporeal administration with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

(http://www.fda.gov/cder/foi/label/1999/20969lbl.pdf)

### VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum (see Appendix A).

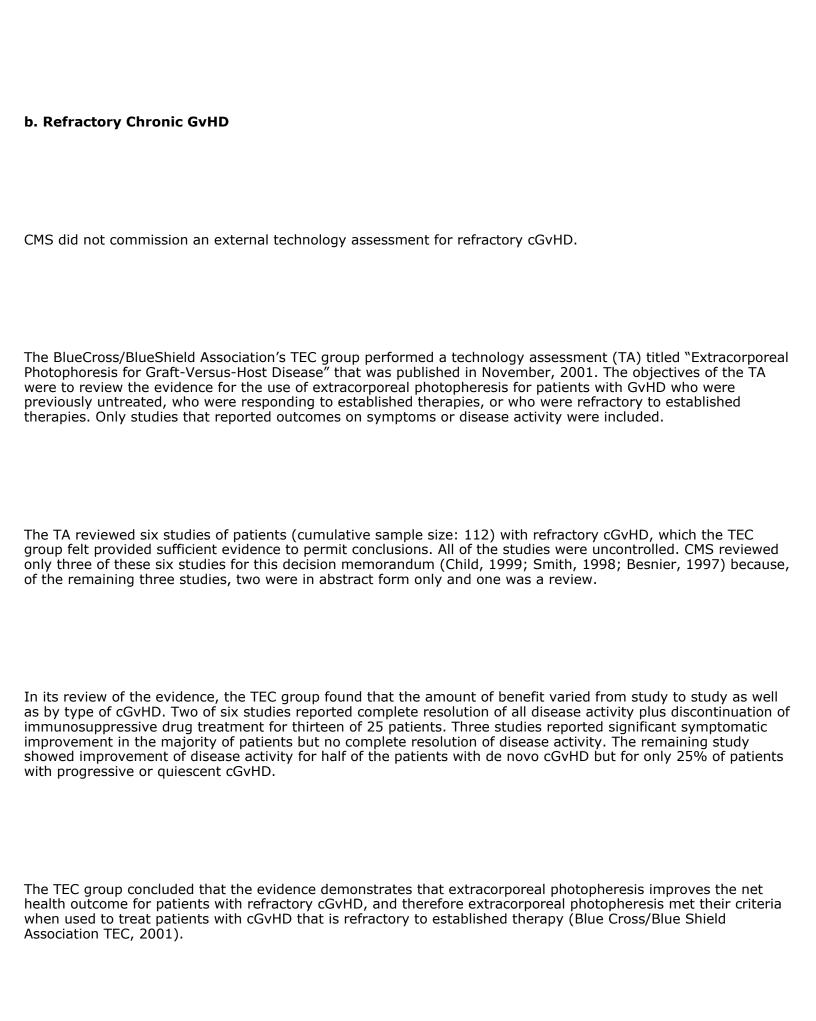
#### VII. Evidence

A. Introduction
This section provides a summary of the evidence that CMS considered during the review. CMS will consider additional evidence submitted during the public comment period.
No randomized controlled clinical trials were found that investigated the use of extracorporeal photopheresis in patients with acute cardiac allograft rejection and cGvHD that is refractory to conventional immunosuppressive therapy. Additionally, there were no randomized controlled clinical trials found that investigated the use of extracorporeal photopheresis in pemphigus vulgaris or bullous pemphigoid. The evidence reviewed for this decision memorandum, therefore, consists of results from uncontrolled clinical trials and case studies that were published in a full length literature article.
B. Discussion of evidence
1. Questions
Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with acute cardiac allograft rejection that is refractory to standard immunosuppressive drugs?
Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with cGvHD that is refractory to standard immunosuppressive drugs?

Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with Bullous Pemphigoid and Pemphigus Vulgaris?
Outcomes:
1) Refractory Acute Cardiac Allograft Rejection
The goal of therapy is to eliminate the immunological attack on the heart. The primary outcome measured in the clinical studies and case studies that were reviewed for this decision memorandum was the change in the histology of serial endomyocardial biopsies. One clinical study also measured the change in the dose of the various drugs administered for immunosuppression. The EMB-focused outcome measures the impact of extracorporeal photopheresis on the severity of the immunological attack, which is a treatment effect. An outcome such as the change in immunosuppressive drug dose also measures a treatment effect.
None of the studies reviewed for this decision memorandum included health outcomes actually experienced by the patient, such as mortality or change in quality of life. However, an improvement in the rejection status with a concomitant reduction of immunosuppression drug doses can result in an improved clinical outcome if it leads to less risk of graft failure and infection (and cancer in the long term).
2) Refractory Chronic GvHD

The goal of therapy is to eliminate the immunological attack on the body. This attack can manifest in a variety of ways. For example, the main manifestation may be only cutaneous, or only pulmonary. Alternatively, a patient may experience the cutaneous, pulmonary, and hepatic manifestations of cGvHD. Accordingly, the assessment of the effects of treatment with extracorporeal photopheresis in patients with refractory cGvHD is dependent on the manifestations of the disease. The primary outcome measured in the clinical studies and case studies that were reviewed for this decision memorandum was the response rate. A positive response meant that there was a decrease in the activity of disease. The appearance (e.g., skin) or the function (e.g., blood liver function tests) of each part of the body involved by cGvHD was noted before and after treatment with extracorporeal photopheresis and then a response rate was calculated. The change in the dose of each immunosuppressive drug was also typically determined. A few of the studies also examined survival.
Survival is a health outcome actually experienced by the patient, which is the type of outcome that CMS prefers. Another health outcome is quality of life. It is possible that a positive response rate, especially regarding the cutaneous effects of cGvHD, which can significantly decrease a patient's quality of life, can result in an improved clinical outcome for the patient. Additionally, an improvement in disease activity due to extracorporeal photopheresis, even if it is less than a total resolution of disease activity, with a concomitant reduction of immunosuppression drug doses may result in an improved clinical outcome if it leads to less risk of infection. However, it is also possible that improved response rates, while improving quality of life, could also have negative effects on survival.
3) Bullous Pemphigoid and Pemphigus Vulgaris
The effects of treatment with photopheresis in patients with pemphigoid/pemphigus are assessed clinically for complete remission (absence of skin or mucous membrane lesions) or disease-free remission, a positive clinical response and decreased serum antibody levels. This is measured in relation to the type of drug/treatment and dosage.
2. External technology assessment
a. Refractory Acute Cardiac Allograft Rejection

For refractory acute cardiac allograft rejection, CMS did not commission an external technology assessment. Printed on 4/13/2012. Page 13 of 52



c. Bullous Pemphigoid and Pemphigus Vulgaris
For bullous pemphigoid and pemphigus vulgaris, CMS did not commission an external technology assessment.
3. Internal technology assessment
a. Evidence Collection
1) Refractory Acute Cardiac Allograft Rejection
For refractory acute cardiac allograft rejection, CMS performed a literature search using PubMed to find clinical trials or meta-analyses evaluating the use of extracorporeal photopheresis in the treatment of patients with acute cardiac transplantation rejection refractory to standard immunosuppressive drugs. The search terms used were 'graft rejection," "heart transplantation," and "photopheresis." The search was limited to the English language and specific for the human population.
CMS also reviewed the information submitted by the NCD requestor. This evidence consisted of eleven published articles of which only one, a case study, reported health-related outcomes around the use of extracorporeal photopheresis to treat patients with acute cardiac transplantation rejection (Lehrer, 2001). Of the remaining ten articles, seven provided background information about cardiac transplantation, heart failure or immunosuppression. The other three articles, which provided either expert opinion about extracorporeal photopheresis or a clinical trial regarding the use of extracorporeal photopheresis to prevent acute cardiac allograft rejection, are presented in the Expert Opinion section of this decision memorandum.

#### 2) Refractory Chronic GvHD

CMS performed a literature search using PubMed to find clinical trials or meta-analyses evaluating the use of extracorporeal photopheresis in the treatment of Medicare patients with cGvHD refractory to standard immunosuppressive drugs. The use of extracorporeal photopheresis for the treatment of aGvHD or for the prevention of cGvHD was not reviewed for this NCD. The search terms used were "graft vs. host disease," or "graft vs. host reaction," and "photopheresis." The search was limited to the English language and specific for the human population.

CMS reviewed the information submitted by the NCD requestor. This evidence consisted of eight published articles of which four reported the health-related outcomes of a clinical trial about the use of extracorporeal photopheresis to treat patients with steroid-resistant or refractory cGvHD (Foss, 2005; Ilhan, 2004; Child, 1999; Greinix, 1998), of the remaining four articles; one presented a study that examined the immunologic mechanism of action of extracorporeal photopheresis. The other three articles are presented in the Expert Opinion section of this decision memorandum.

CMS also reviewed the information submitted in a public comment by Therakos, Inc. Of the nineteen published full length articles contained in the public comment that reported the health-related outcomes of a clinical trial or meta-analysis or case study in adult patients treated with extracorporeal photopheresis for cGvHD but were not already submitted by the requestor, seven were clinical trials (Garban, 2005; Couriel, 2005; Rubegni, 2005; Apisarnthanarax, 2003; Seaton, 2003; French, 2002; Smith, 1998) and one was a case study in patients with refractory cGvHD (Besnier, 1997).

Of the remaining eleven articles, eight provided background about cGvHD or the mechanism of action of extracorporeal photopheresis or information about the use of extracorporeal photopheresis in patients who did not have cGvHD. The other three articles are presented in the Expert Opinion section of this decision memorandum.

A Blue Cross/Blue Shield TEC technology assessment from 2001 was also submitted in the public comment. This technology assessment is presented in the External Technology Assessment section of this decision memorandum.

3) Bullous Pemphigoid and Pemphigus Vulgaris
CMS performed a literature search using PubMed to find any peer reviewed journal literature evaluating the use of extracorporeal photopheresis in the treatment of patients with PV or PB. The search terms used were ("Pemphigus"[MeSH Major Topic] OR "Pemphigoid, Bullous"[MeSH Major Topic] OR "Pemphigoid, Benign Mucous Membrane"[MeSH Major Topic]) AND ("Immunotherapy"[MeSH Major Topic] OR "Photopheresis"[MeSH Major Topic]).
CMS also reviewed the information submitted by the NCD requestor, and examined a TA by Blue Cross/Blue Shield. The resulting literature we reviewed including the submissions by the requesters is as follows:
Published full length articles that were not submitted by the requesters included one review article by Shih WY, Sami N and Razzaque AA (2005) and a TA (BC/BS 2006 update).
Articles submitted by the requesters included two single-case reports (Gollnick HPM et al. 1993, Liang G, Nahass G, Kerdel FA. 1992), one 4-case report (Rook AH et al. 1990), and a non-controlled trial of 7 patients (Wollina U, Lange D, Looks A. 1999).
b. Evidence Summary
1) Refractory Acute Cardiac Allograft Rejection
<u>Clinical Trials</u>

Printed on 4/13/2012. Page 17 of 52

Five clinical trials evaluating the use of extracorporeal photopheresis in the treatment of patients with acute cardiac allograft rejection refractory to standard immunosuppressive drugs were identified.

Dall'Amico R, Montini G, Murer L, et al. Extracorporeal photochemotherapy after cardiac transplantation: a new therapeutic approach to allograft rejection. International Journal of Artificial Organs 2000;23:49-54

This was a prospective, uncontrolled study conducted in eleven patients with a history of two or more grade 3A-3B acute rejection episodes during the three months prior to extracorporeal photopheresis despite standard immunosuppression therapy regimen extracorporeal photopheresis was performed as 2 consecutive daily treatments each week for one month, then two treatments biweekly for two months, then two treatments monthly for three months using the UVAR system and 200 micrograms of 8-MOP administered ex vivo. The change in EMB histology was the measured health outcome. A grade of 0 or 1A was considered to represent complete resolution of rejection.

Five men and six women were in the study. The age range was 35 to 65 years. One patient died during the sixmonth treatment period due to hepatitis C infection (details not provided) and one patient dropped out due to a relapse of rejection that was unresponsive to extracorporeal photopheresis and high doses of steroids. For the nine patients who completed six months of extracorporeal photopheresis treatment, all episodes of rejections were reversed after a mean time of 14.2 days (range 7-32 days). The changes in the EMB results are shown in the following table.

## Change in EMB Results (n= 11 patients)

Histological Grade	Pre-extracorporeal photopheresis (% of biopsies; n= 110 biopsies)	During extracorporeal photopheresis (% of biopsies; n= 78 biopsies)
Negative (Grade 0)	25	27
1A	21	45

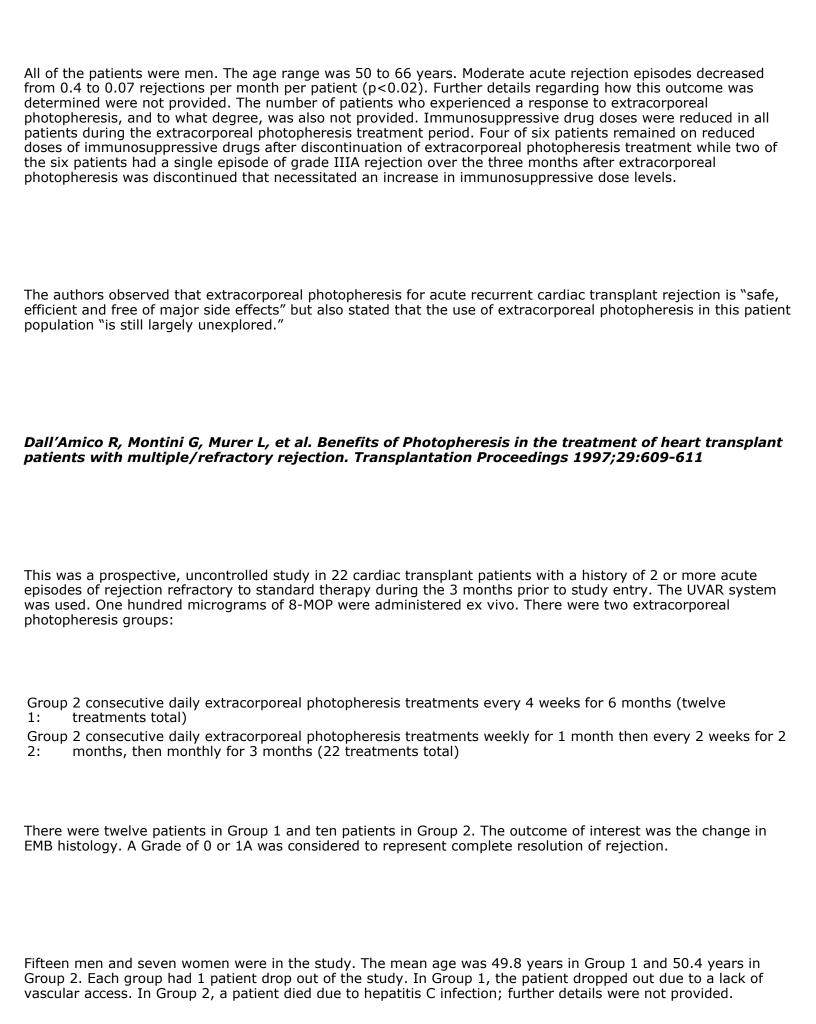
Histological Grade	Pre-extracorporeal photopheresis (% of biopsies; n= 110 biopsies)	During extracorporeal photopheresis (% of biopsies; n= 78 biopsies)
18	6	2
2	6	8
3A	29	17
3B	13	1

Six of nine patients experienced a rejection relapse during the sixty-month follow-up period after extracorporeal photopheresis. Of these, four episodes were reversed with the resumption of extracorporeal photopheresis (details not provided by the authors), one episode was reversed using high-dose steroids, and one episode was reversed with methotrexate after failure of extracorporeal photopheresis and high-dose steroids. During extracorporeal photopheresis there was one case of interstitial pneumonia and one case of symptomatic hypotension in a patient with pre-existing anemia and low body weight.

The authors stated that "despite the efficacy and safety reported...extracorporeal photopheresis cannot be recommended for the treatment of all rejection episodes. Most allograft rejections are easily reversed by an inexpensive course of IV steroids and rejection relapses are observed only in a limited number of cases." Furthermore, the authors suggest extracorporeal photopheresis may be indicated "for the treatment of allograft rejection in patients needing a reduction in standard immunosuppression because of complications such as severe infections, nephrotoxicity, obesity, osteopenia...and in recipients with refractory and recurrent rejections."

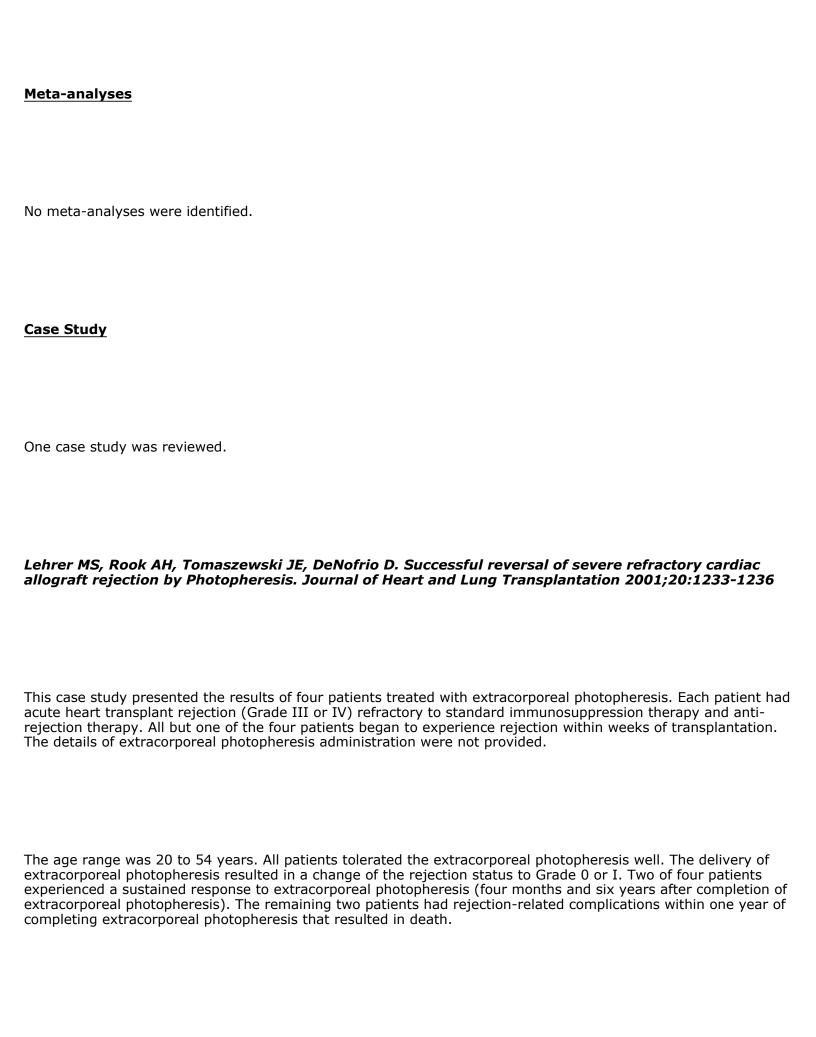
Giunti G, Schurfeld K, Maccherini M, et al. Photopheresis for recurrent acute rejection in cardiac transplantation. Transplantation Proceedings 1999;31:128-129

In Giunti, 1999 a prospective, uncontrolled trial with six patients with a history of recurrent acute rejection despite daily triple immunosuppressive therapy was conducted. Extracorporeal photopheresis using the UVAR system and 200 micrograms of 8-MOP administered ex vivo was performed on 2 consecutive days weekly for 1 month, then once weekly for 1 month, then biweekly for 2 months, and then monthly for 2 months. The change in EMB histology was the measured outcome.



Nine of eleven patients in Group 1 had resolution of rejection while all nine patients in Group 2 had resolution. The mean time to resolution was 29.5 days in Group 1 and 13.8 days in Group 2.
The mean number of relapses of rejection per patient during 6 months of extracorporeal photopheresis was 1.36 in Group 1 and 0.8 in Group 2. The number of courses of steroid-based rejection therapy used to treat the relapse was seven in Group 1 and one in Group 2. The number of courses of methotrexate-based rejection therapy used to treat the relapse was one in Group 1 and one in Group 2.
One patient in Group 1 experienced a herpes zoster infection. One patient in Group 2 developed interstitial pneumonia, and one patient with pre-existing anemia and low body weight had symptomatic hypotension during an extracorporeal photopheresis procedure.
The authors highlighted that a higher frequency of treatment (as given in Group 2) was associated with a lower number of rejection relapses and hence a corresponding decrease in immunosuppressive drug therapy. They concluded that extracorporeal photopheresis "could be considered safe and efficacious treatment for patients with repeated rejection episodes," that a more aggressive treatment protocol is advisable, and that "increased clinical experience is necessary to evaluate and individualize frequency of treatment."
Dall'Amico R, Livi U, Milano A, et al. Extracorporeal photochemotherapy as adjuvant treatment of heart transplant recipients with recurrent rejection. Transplantation 1995;60:45-49
The authors performed a prospective, uncontrolled study in eight cardiac transplant patients with a history of multiple acute rejection episodes despite a routine immunosuppression regimen. The UVAR system was used. Two hundred micrograms of 8-MOP was administered ex-vivo. Extracorporeal photopheresis was performed on 2 consecutive days every 4 weeks for 6 months. The outcomes measured were change in EMB histology, and the change in the dose of each immunosuppressive drug.

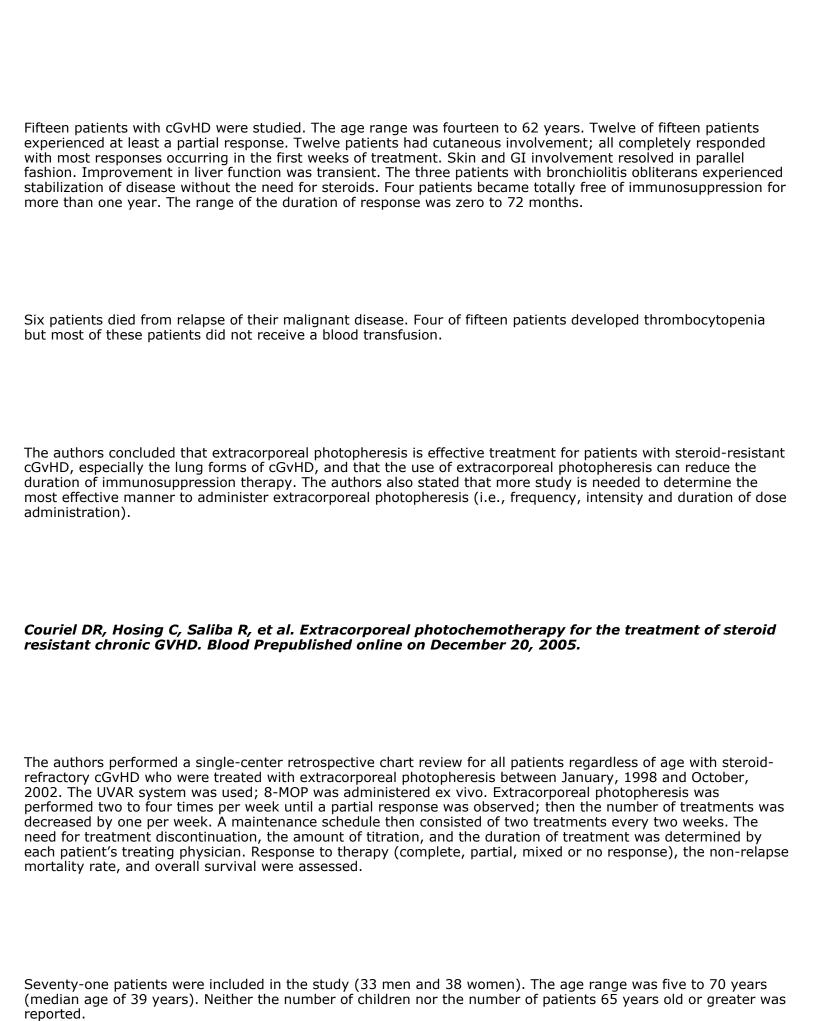








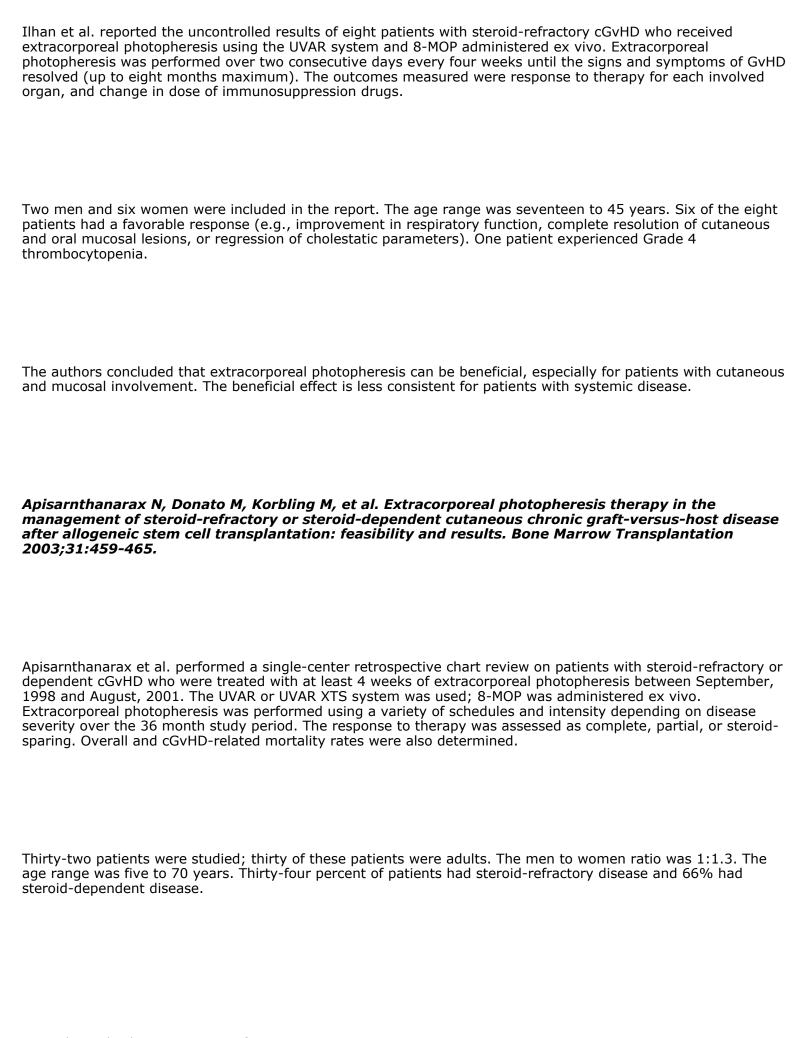
Printed on 4/13/2012. Page 25 of 52



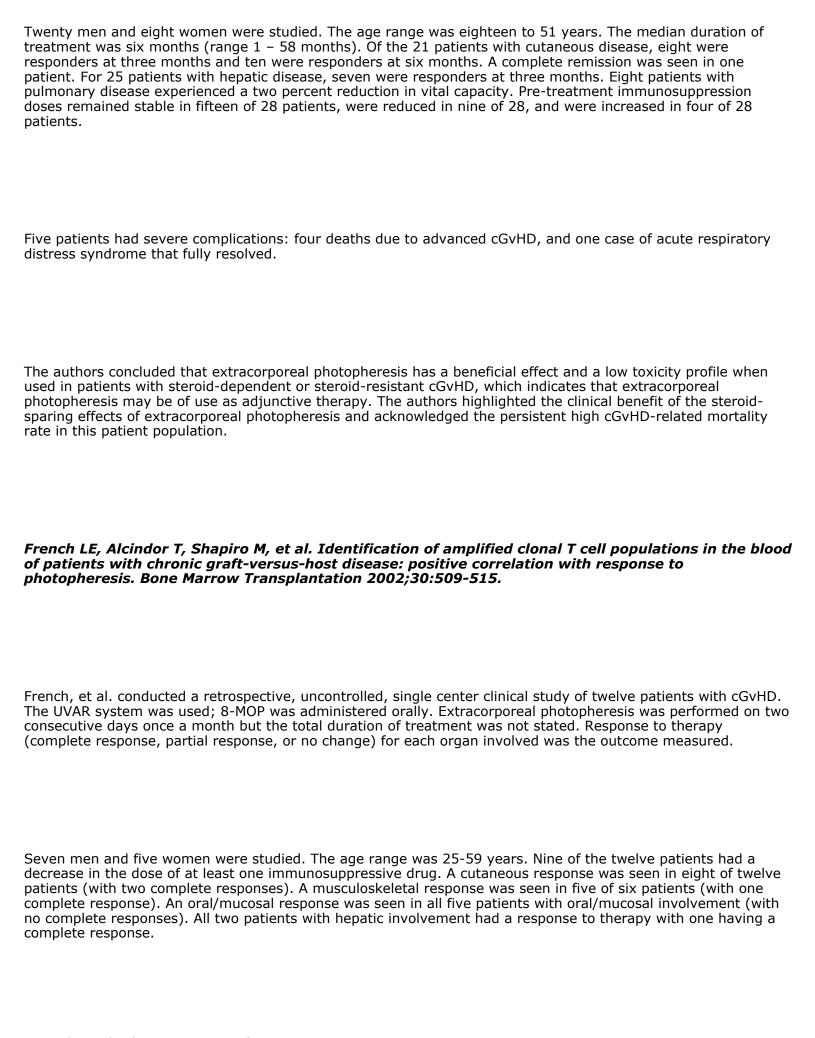
Printed on 4/13/2012. Page 26 of 52



An overall outcome score was calculated in an attempt to assess the role of extracorporeal photopheresis in the context of concomitant therapies for cGvHD. The following categories were used when considering the contribution of extracorporeal photopheresis: Determinant complete response seen in all involved organs plus a fifty percent or greater reduction in immunosuppression use Good status assigned if outcome is between determinant and ineffective Ineffective disease progression seen in an organ, or there was a need to increase immunosuppression, or complete response not seen in any organ plus immunosuppression was not reduced by fifty percent or greater An overall outcome of Determinant or Good was given a score of one and classified as a response; an overall outcome of Ineffective was given a score of zero and classified as a non-response. Thirty-two patients were studied (twenty men and twelve women). The age range was eighteen to 60 years. Seventy-eight percent of the patients were responders (22% Determinant, 56% Good); 22% of patients were non-responders. Minor side effects such as hypotension, and venipuncture site hematomas were noted. The authors concluded that overall extracorporeal photopheresis is a beneficial treatment for patients with steroid -refractory cGvHD. Extracorporeal photopheresis was particularly effective for patients with thrombocytopenia but less effective for patients with the lung forms of disease. Ilhan O, Arat M, Arslan O, et al. Extracorporeal photoimmunotherapy for the treatment of steroid refractory progressive graft-versus-host disease. Transfusion and Apheresis Science 2004;30:185-*187.* 

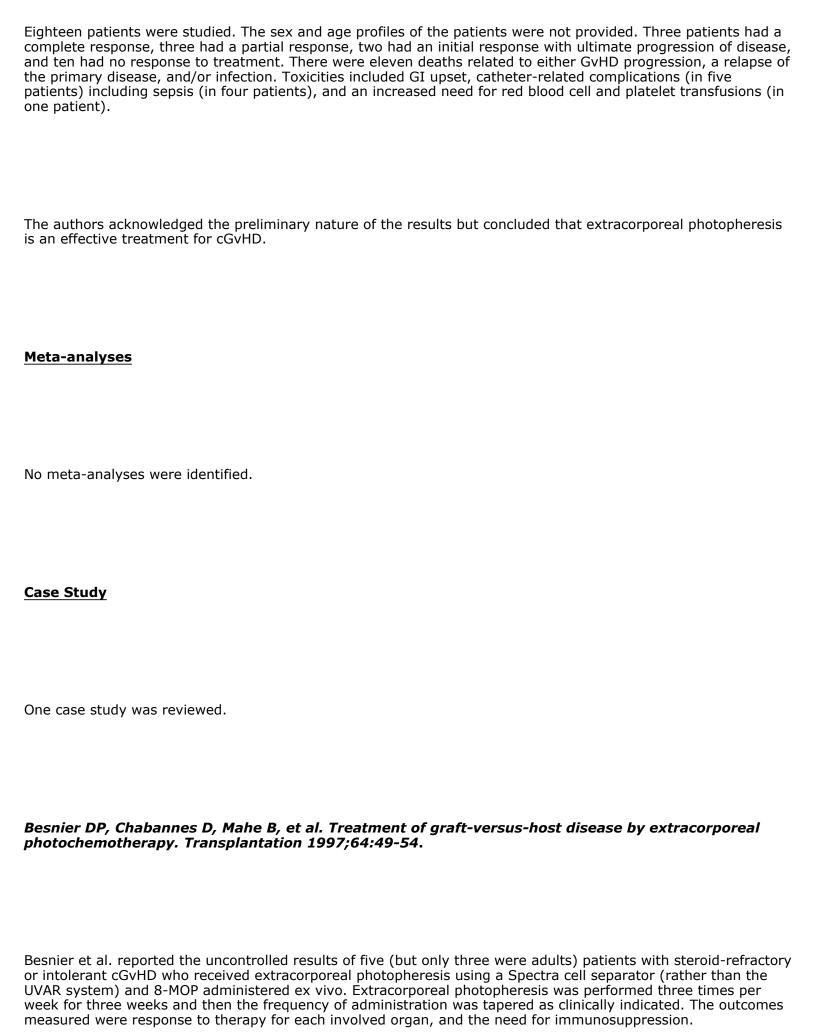




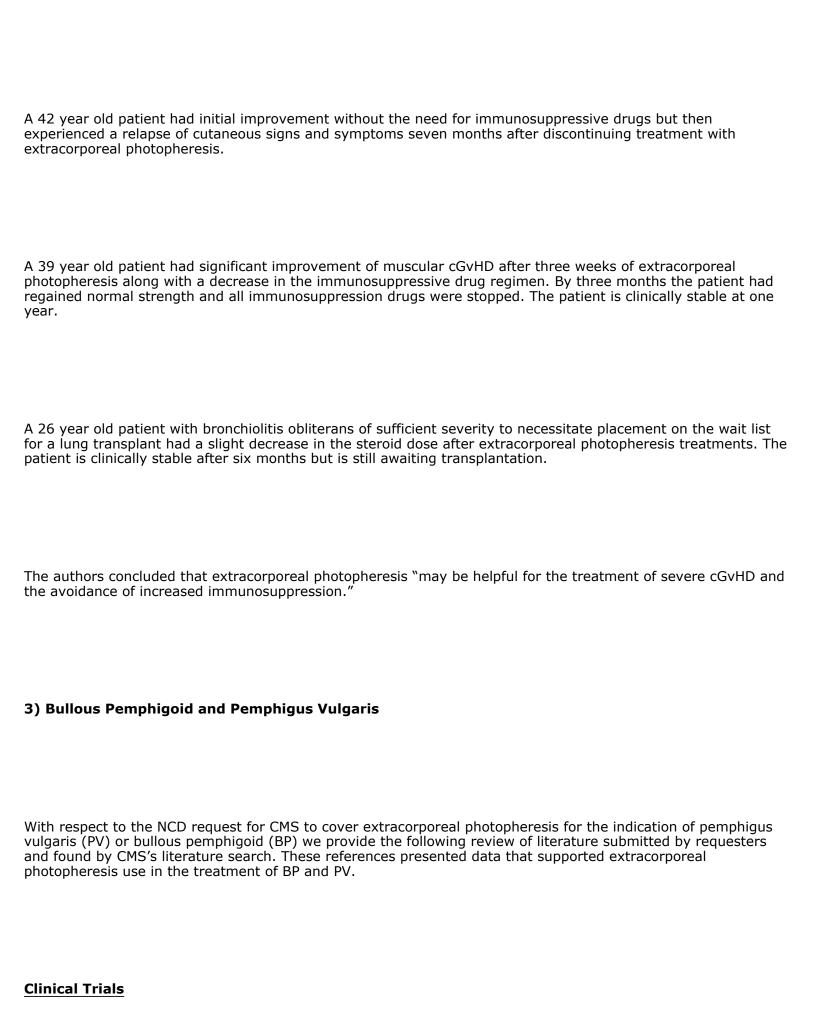




Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood 1998;92:3098-3104.
The article by Greinix et al. reports on the uncontrolled results of fifteen consecutive patients with refractory cGvHD that were treated with extracorporeal photopheresis using the UVAR system and 8-MOP administered ex vivo. Extracorporeal photopheresis was performed on two consecutive days every two weeks for three months and then every four weeks until there was resolution of sign and symptoms of cGvHD. The outcomes measured were response to therapy for each involved organ (complete response, partial response, no change, or no response), and survival.
All fifteen patients with cutaneous involvement had a response (twelve with a complete response). All four patients with musculoskeletal involvement had a response (no complete responses). All eleven patients with oral/mucosal involvement had a complete response. For ten patients with hepatic involvement, nine had a response (seven with a complete response). Five of six patients with ocular involvement had a response (one complete response). Two of three patients with thrombocytopenia had a response (two complete responses). Fourteen patients were alive after a median follow-up of fifteen months; the one death was due to a relapse of the primary disease.
The authors concluded that extracorporeal photopheresis has "some efficacy in the treatment of drug-resistant chronic GvHD, with minor overall toxicity."
Smith EP, Sniecinski I, Dagis AC, et al. Extracorporeal photochemotherapy for treatment of drug- resistant graft-versus-host disease. Biology of Blood and Marrow Transplantation 1998;4:27-37.
This was a prospective, uncontrolled, single center, clinical study in patients with refractory cGvHD who were given extracorporeal photopheresis using the UVAR system. 8-MOP was administered orally and the dose was adjusted based on serum levels. Extracorporeal photopheresis was performed on two consecutive days every three weeks and then two to three times per week. The frequency of treatment was then modified on an individual basis. While the main goal was to study the characteristics of the T lymphocytes both before and after extracorporeal photopheresis, a response to therapy for each involved organ was measured as complete response, partial response, or no response.



Printed on 4/13/2012. Page 34 of 52



Wollina et al. reported a 7- person no control group trial having 4 females 3 three males, with three different autoimmune types of bullous disease (PV, BP, and pemphigus foliaceous) (Wollina et al. 1999). Pemphigus foliaceous is defined as chronic pemphigus in which extensive scaling dermatitis, with no perceptible blistering, may be present in addition to the bullae. With varying follow-up times ranging from 4 -42 months, they reported partial or complete remission secondary to extracorporeal photopheresis treatment with varying numbers of treatment cycles. Complete remission was defined as elimination of all cutaneous and mucous membrane blisters and erosions, while partial remission was indicated to be improvement but not complete elimination of those lesions. Details on these patients are listed in the following table.

Clinical characteristics and outcome in patients with pemphigus or BP treated with adjuvant extracorporeal photopheresis									
Patient	Age (yrs)	Sex	Diagnosis	Disease Duration (months)	Drugs	extracorporeal photopheresis Cycles	Response	Follow-up (months)	
1	44	М	PV	12	100mg pred	2	CR	24	
2	48	М	PF	36	15mg pre/150 mg aza	8	PR	33	
3	85	F	ВР	5	100mg pred	1	CR	32	
4	83	F	ВР	24	100mg pred	4	CR	42	
5	44	F	PV	2	200mg pred	2	CR	34	
6	70	М	ВР	3	200mg pred/150 mg aza	2	CR	4	
7	31	F	PV	3	100mg pred	3	CR	10	

PF = Pemphigus Foliaceous; pred = prednisolone; aza = azathiaprine; CR=complete remission; PR=partial remission



Not applicable.
5. Evidence-based guidelines
No evidence-based guidelines were identified for the use of extracorporeal photopheresis for refractory acute cardiac allograft rejection, refractory cGvHD, or bullous pemphigoid and pemphigus vulgaris.
6. Professional Society Position Statements
None found.
7. Expert Opinion
For refractory acute cardiac allograft rejection, the NCD requestor submitted three published articles that were noted but not evaluated by CMS because they do not report the results of a clinical trial meta-analysis or case study that examined a health-related outcome in adult patients with refractory acute cardiac allograft rejection who were treated with extracorporeal photopheresis. In Dall'Amico, 2002 the authors reviewed the past and current use of extracorporeal photopheresis in patients who have received a transplantation (cardiac or non-cardiac) and noted that extracorporeal photopheresis is effective with a "histological resolution of acute rejectionreported in 89% of cardiac transplant patients" without the typical drug-based immunosuppressive complications. It was also noted that the best way to administer extracorporeal photopheresis is still to be determined. In an editorial about the use of extracorporeal photopheresis for the prevention of cardiac allograft rejection (Barr, 2003), the difficulties with using drug-based immunosuppression as well as the clinical history of extracorporeal photopheresis use were presented. The author stated that "present and future studies will help to define the role of this novel, safe, and non-toxic, immunomodulating technology in the field of transplantation." In a clinical trial about the use of extracorporeal photopheresis to prevent acute cardiac allograft rejection (Barr, 1998), the authors found that adding extracorporeal photopheresis to a standard immunosuppressive drug regimen decreased the risk of the onset of acute rejection without increasing the incidence of infection.

For refractory cGvHD, the NCD requestor submitted three articles that were noted but not evaluated by CMS because they do not report the results of a clinical trial or meta-analysis or case study that examined a health-related outcome in adults. In Foss, 2003 the authors reviewed the mechanism of action and clinical efficacy of extracorporeal photopheresis for patients with cGvHD and noted that extracorporeal photopheresis has been shown to be an effective therapy for patients with cGvHD. Dall'Amico et al. (2002) reviewed clinical studies of extracorporeal photopheresis conducted in patients with refractory cGvHD. They concluded that extracorporeal photopheresis should be considered as a second-line therapy for patients with refractory cGvHD, and that randomized clinical trials are needed to confirm the efficacy of extracorporeal photopheresis. In Coyle, 2004 the results of a clinical trial of extracorporeal photopheresis in pediatric patients with cGvHD were briefly presented. The authors concluded that extracorporeal photopheresis improves the cutaneous manifestations of cGvHD and decreases drug immunosuppression use in a subset of patients.

Therakos, Inc. submitted two review articles about extracorporeal photopheresis (Komanduri, 2006; Sniecinski, 2000) and one article that presented the results of a clinical trial in pediatric patients with cGvHD (Dall'Amico, 1997). Komanduri et al. reviewed the available clinical and non-clinical studies of extracorporeal photopheresis in GvHD and noted that prospective randomized clinical trials "may be required to clearly establish the role of extracorporeal photopheresis." In Sniecinski, 2000 the authors reviewed the role of extracorporeal photopheresis in the treatment of patients with cGvHD and concluded that extracorporeal photopheresis ideally should be used before second-line immunosuppressive drugs, which can mask the immunomodulatory effects of extracorporeal photopheresis. They also called for randomized clinical trials that study the efficacy of the early use of extracorporeal photopheresis. Dall'Amico et al. (1997) studied pediatric patients with refractory cGvHD and concluded that extracorporeal photopheresis is a "non-aggressive" treatment that may benefit some patients with refractory cGvHD.

### 8. Public Comment

#### **30-day Initial Public Comment Period**

During the initial 30-day public comment period, CMS received comments from twenty-one individuals and organizations. All commenters advocate for the expansion of CMS' current policy of extracorporeal photopheresis for cGvHD. Comments are available entirely at <a href="http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca">http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca</a> id=180

CMS received twelve comments from individuals from Universities/Medical centers. Seven commenters from this group support cGvHD alone; one commenter supports cGvHD and Nephrogenic Fibrosis Dermopathy/Nephrogenic Systemic Sclerosis; two commenters support cGvHD and refractory cardiac graft rejection; one commenter supports cardiac transplant rejection; cGvHD; and autoimmune blistering diseases (pemphigus and bullous pemphigoid); and one commenter advocates for several categories in support of cGvHD. One public commenter noted that American Society of Apheresis (ASFA) created a new ASFA approach to assignment of categories for creatment based on the principles of evidence based medicine, and submitted a draft statement. Regarding the indications addressed in this NCD, ASFA places cutaneous cGvHD and cardiac allograft rejection (acute or chronic was not distinguished) in category II, which means that there is sufficient evidence to suggest efficacy usually as adjunctive therapy. Additionally, ASFA places non cutaneous cGvHD and pemphigus vulgaris in category III, which means that there is inconclusive evidence of efficacy or uncertain risk/benefit ratio. The commenter also

## Comments from Hospitals/Clinics

CMS received seven comments from individuals from Hospitals/Clinics. Of this group, three commenters support cGvHD alone; four commenters support cGvHD and solid organ graft rejection; one commenter supports refractory rejection/antibody mediated rejection; one commenter supports transplant rejection for cardiac and other organs; cGvHD, bone marrow or allogeneic stem cell transplantation; and progressive systemic scleroderma; and one commenter supports scleroderma, cGvHD, lung & cardiac transplant, and nephrogenic fibrosing dermopathy.

## Comments from General Public

CMS received from a patient who is in favor of cGvHD alone. The patient stated that extracorporeal photopheresis improved his immune system and quality of life. In addition, CMS received a comment from one company that also supports cGvHD alone.

#### **VIII. CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a
particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In
order to be covered by Medicare, an item or service must fall within one or more benefit categories contained
within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions,
the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of
illness or injury or to improve the functioning of a malformed body member" § 1862(a)(1)(A).

In analyzing the evidence, CMS asked is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with:

- · acute cardiac allograft rejection that is refractory to standard doses of immunosuppressive drugs,
- cGvHD that is refractory to standard doses of standard immunosuppressive drugs, and
- bullous pemphigoid and pemphigus vulgaris?

The evidence available to support the use of extracorporeal photopheresis in patients with these severe immunological disorders comes from small uncontrolled clinical trials and case studies. The studies of bullous pemphigoid and pemphigus vulgaris were exclusively very small case studies. A controlled clinical trial is the preferred trial design because it provides standardized treatment regimen (e.g., the frequency, intensity, and duration of extracorporeal photopheresis administration) and assessment methods, and a comparison group. These features are designed to prevent the introduction of bias and the confounding of the data.

The vast majority of patients studied were not of Medicare age (i.e., 65 years of age or older) however this is less of a concern with post-transplantation patients because Medicare provides for the pre-operative and post-operative care for patients in the Medicare program who have received a heart or allogeneic hematopoietic cell transplantation regardless of age.

CMS considered the requestors suggestion that local Medicare contractors be permitted discretion to cover other conditions such as pemphigus foliaceous, acute graft versus host disease, systemic sclerosis and rejection of other transplanted solid organs, but found insufficient evidence to warrant proposing contractor discretion.

#### 1) Refractory Acute Cardiac Allograft Rejection

The evidence available to support the use of extracorporeal photopheresis in patients with refractory acute cardiac allograft rejection comes from five prospective clinical trials and from a case study. The fifth clinical trial (Dall'Amico, 1997) included a modicum of control by having two groups of patients with each group receiving a different cumulative dose of extracorporeal photopheresis. The remaining four clinical trials were uncontrolled, which may have impacted the quality of the results generated by these trials by potentially introducing significant bias and confounding the data. All five clinical trials as well as the case study were small in sample size. The various extracorporeal photopheresis treatment protocols used (e.g., frequency and duration of extracorporeal photopheresis administration, 8-MOP formulation) throughout the studies is an additional design issue that prevents pooling of the evidence in an attempt to overcome the small sample size of each study.

Notwithstanding the study design concerns, the results from the clinical studies do show a benefit to performing extracorporeal photopheresis in patients with refractory acute cardiac allograft rejection. In Dall'Amico, 1997, the authors reported a greater than 80% response rate within one month of initiating extracorporeal photopheresis. A dose-response relationship was also exhibited where the group that received more extracorporeal photopheresis treatments had a higher response rate and a shorter time to response.. The duration of response was not stated. In an article published in 2000, Dall'Amico et al. noted a 100% response rate. In Dall'Amico, 1995 the need for reduced doses of immunosuppressive drugs was shown.

While the evidence suggests that there is a short term benefit of extracorporeal photopheresis, the long term benefits have not been demonstrated in this patient population. In fact, while the patients in Dall'Amico, 2000 experienced a 100% response rate to extracorporeal photopheresis, there was also a 67% rate of relapse of disease after extracorporeal photopheresis was discontinued. The remaining studies apparently did not study, or at least report, the long term effects of extracorporeal photopheresis. Hence, questions remain regarding the most appropriate way to administer extracorporeal photopheresis to patients with refractory acute cardiac allograft rejection.

A safety problem was not demonstrated in any of the studies beyond the known complications associated with the extracorporeal photopheresis procedure (e.g., transient hypotension). In Dall'Amico, 1997 the patients who received 22 extracorporeal photopheresis treatments did not appear to experience greater toxicity than the patients who received twelve treatments. In Dall'Amico, 2000, the patients were followed for 60 months after discontinuation of extracorporeal photopheresis treatments without any mention of extracorporeal photopheresis-related toxicity. However, attempts to associate side effects or complications with extracorporeal photopheresis are confounded by the concurrent use of immunosuppressive drugs, by the general clinical status of the patient, and in general by the lack of a control group for comparison.

Acute cardiac allograft rejection that has not responded to multiple attempts with multiple immunosuppressive drugs is a life-threatening disease that affects a small number of patients. Despite limitations in the evidence, the studies evaluated in this decision memorandum demonstrate that extracorporeal photopheresis improves some health outcomes for patients without an obvious sign of significant toxicity in patients with a disease process that has no alternative treatment. Therefore, CMS believes that the evidence is sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with acute cardiac allograft rejection that is refractory to standard immunosuppressive drugs. Based upon the above findings, extracorporeal photopheresis is reasonable and necessary for patients of any age with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment.

## 2) Refractory Chronic GvHD

The evidence to support the use of extracorporeal photopheresis in patients with cGvHD that is refractory to standard immunosuppressive drugs was derived from eleven clinical trials, five of which were prospective, and one case study. All of the trials were uncontrolled trials so there is an increased risk of assessment bias and data confounding. The small sample size of each trial (with the exception of Couriel, 2005) may have also impacted the overall quality of the evidence, especially given the highly variable extracorporeal photopheresis treatment protocol used in each trial.

Despite the identified study design limitations, the evidence demonstrates some benefit of extracorporeal photopheresis in this patient population. Foss et al. reported a clinical response rate of 64% while Couriel et al. reported a 61% clinical response rate and Rubegni et al. noted a 78% response rate. The benefits, however, vary by organ of involvement. The most prominent and consistently reported improvement is for the cutaneous manifestations of cGvHD (Foss, 2005; Ilhan, 2004; French, 2002; Child, 1999; Greinix, 1998). The oral/mucosal manifestations also improve with extracorporeal photopheresis treatment (Ilhan, 2004; French, 2002; Greinix, 1998). Improvement of the systemic manifestations of cGvHD (e.g., liver or lung function), however, was not clear from the evidence (Seaton, 2003). There is also some evidence that extracorporeal photopheresis leads to decreased doses of immunosuppressive drugs (Apisarnthanarax, 2003; French, 2002).

Relapse of cGvHD was not widely reported. However, it is not possible to evaluate the durability of the benefits of extracorporeal photopheresis due to the short duration of follow-up and the highly variable extracorporeal photopheresis administration schedule used in each clinical trial. For example, in Couriel, 2005, after the administration of a standard extracorporeal photopheresis regimen each patient's physician was permitted to decide both the need for continuation of extracorporeal photopheresis treatment and the treatment frequency.

An obvious safety concern during the actual extracorporeal photopheresis procedure is not evident from the evidence. Patient mortality, as noted in the Seaton, 2003 and Smith, 1998 studies, is still a significant issue. However, since cGvHD is a life-threatening disease, it is not possible to discern if the high mortality is due to the disease (including the multiple toxic immunosuppressive drugs that the patient is taking) or due to extracorporeal photopheresis. In addition, the small sample size and the lack of a control group for comparison in each study prevent a determination of whether the death is due to inevitable disease progression or due to extracorporeal photopheresis.

Chronic GvHD that has not responded to multiple attempts with multiple immunosuppressive drugs is a life-threatening disease with a lack of alternative treatments that occurs in a small number of patients. Despite limitations in the evidence, it demonstrates some improved health outcomes for patients treated with extracorporeal photopheresis, particularly for the cutaneous and oral/mucosal manifestations of the cGvHD without an obvious sign of significant toxicity. Therefore, CMS believes that the evidence is sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with cGvHD that is refractory to increasing doses of standard immunosuppressive drugs. Based upon the above findings, extracorporeal photopheresis is reasonable and necessary for patients of any age with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

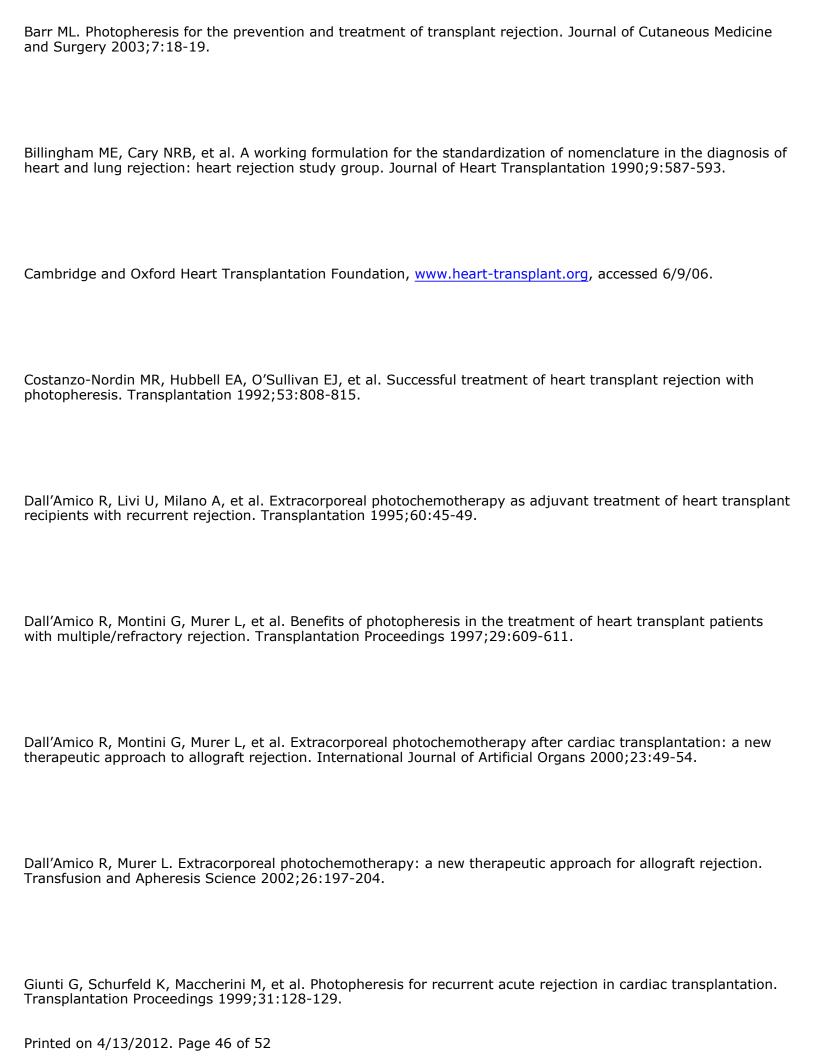
## 3) Bullous Pemphigoid and Pemphigus Vulgaris

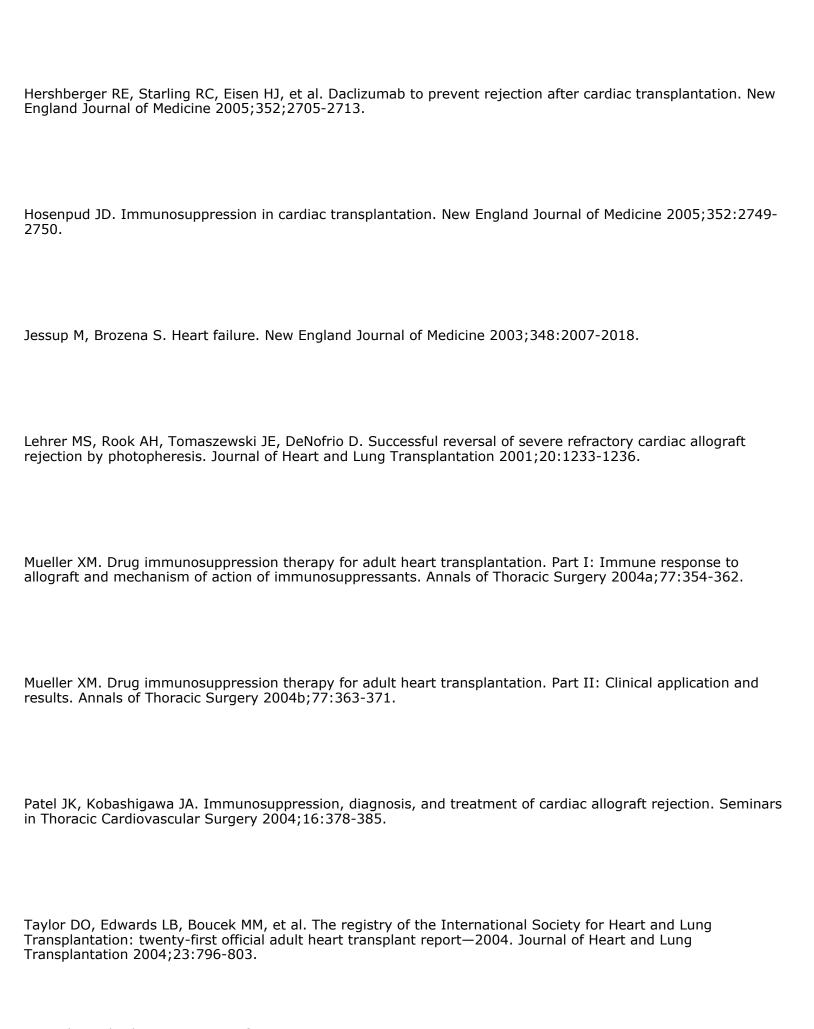
After a complete review of the scientific and clinical evidence regarding extracorporeal photopheresis for PV and BP there was a total of 17 patients. We find that there are very few patients and no control groups. Good data on survival in patients with BP or PV treated by extracorporeal photopheresis are not available. The data is sparse and poor. In the Wollina paper, the authors conclude the following: "short-time adjuvant ECP is a recommendable treatment modality for drug-resistant autoimmune bullous disease. Prospective controlled trials comparing long-term and short-term adjuvant ECP in autoimmune bullous disease are necessary to validate our observations" (Wollina et al., 1999). The one review we found could not recommend extracorporeal photopheresis for PV or BP. Based on the available data, CMS has determined that there is insufficient evidence to conclude that extracorporeal photopheresis treatment for bullous pemphigoid and pemphigus vulgaris will improve health outcomes for Medicare patients in general without limitations. Therefore, CMS has determined that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

#### **IX. Proposed Decision**

The Centers for Medicare and Medicaid Services (CMS) proposes that extracorporeal photopheresis is reasonable and necessary for:

1. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment;
2. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.
CMS proposes that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.
All other indications remain non-covered.
Appendices [PDF, 533KB] Back to Top  Bibliography
Refractory Acute Cardiac Allograft Rejection
Barr ML, Meiser BM, Eisen HJ, et al. Photopheresis for the prevention of rejection in cardiac transplantation. New England Journal of Medicine 1998;339:1744-1751.





# **Refractory Chronic Graft versus Host Disease**

Apisarnthanarax N, Donato M, Korbling M, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. Bone Marrow Transplantation 2003;31:459-465.
Besnier DP, Chabannes D, Mahe B, et al. Treatment of graft-versus-host disease by extracorporeal photochemotherapy. Transplantation 1997;64:49-54.
Blue Cross/Blue Shield Association Tec. Extracorporeal photopheresis for graft-versus-host disease. 2001.
Child FJ, Ratnavel R, Watkins P, et al. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus -host disease (GVHD). Bone Marrow Transplantation 1999;23:881-887.
Couriel DR, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary therapy and supportive care working group report. Biology of Blood and Marrow Transplantation 2006;12:375-396.
Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid resistant chronic GVHD. Blood Prepublished online on December 20, 2005.
Coyle TS, Nam TK, Camouse MM, et al. Steroid-sparing effect of extracorporeal photopheresis in the treatment of graft-versus-host disease. Archives of Dermatology 2004;140:763-764.

